Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease

Policy Number: 2.04.23
Origination: 07/2015
Last Review: 07/2018
Next Review: 07/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease. This is considered not medically necessary.

If the test or procedure is not listed in the member’s list of benefits, and Blue Cross and Blue Shield of Kansas City determines that it was done on an individual without specific symptoms of a condition or disease for which the test was done, it will be considered a non-covered screening test.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Measurement of plasma levels of homocysteine is considered not medically necessary in the screening, evaluation, and management of patients for cardiovascular disease.

Measurement of plasma levels of homocysteine is considered investigational in the screening, evaluation, and management of patients with venous thromboembolism or risk of venous thromboembolism.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: • Who are asymptomatic with risk of cardiovascular disease</td>
<td>Interventions of interest are: • Homocysteine testing</td>
<td>Comparators of interest are: • Routine care without homocysteine testing</td>
<td>Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures</td>
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</table>
Homocysteine is an amino acid that has been evaluated as a potential marker of cardiovascular disease (CVD) and increased risk of thrombosis in the general population and as a potential risk marker for people with CVD and thrombotic disorders. The association between homocysteine-lowering interventions and risk of CVD or thrombotic events has also been examined.

For individuals who are asymptomatic with risk of CVD or who have CVD who receive homocysteine testing, the evidence includes observational studies and randomized controlled trials (RCTs) of homocysteine-lowering interventions. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and CVD risk, especially in patients with preexisting vascular disease. However, evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins improves cardiovascular outcomes. Numerous large RCTs and meta-analyses of these trials have consistently reported that homocysteine-lowering treatment is ineffective in reducing major cardiovascular events. One systematic review of a subgroup analysis from 3 RCTs of patients not on antiplatelets at baseline found that homocysteine-lowering treatment reduced the risk of stroke in that group. However, replication of this effect in countries with grain enriched with folic acid would be needed. Given the large amount of evidence from placebo-controlled RCTs that homocysteine-lowering interventions do not improve health outcomes, it is unlikely that routine homocysteine testing has the potential to change management that improves health outcomes. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who are asymptomatic with risk of venous thromboembolism (VTE) or who have experienced VTE events who receive homocysteine testing, the evidence includes of observational studies and RCTs of homocysteine-lowering interventions. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events.
Observational evidence has generally supported the association between homocysteine levels and VTE risk, although the association was limited to men in the largest prospective study. However, evidence from RCTs evaluating homocysteine-lower interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces risk of VTE. Only 1 RCT was designed to test for VTE as a primary outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

Homocysteine is a sulfur-containing amino acid that is rapidly oxidized in plasma into homocysteine and cysteine-homocysteine disulfide. Measurement of total plasma homocysteine is the sum of homocysteine and its oxidized forms. The laboratory test is referred to as either homocysteine or homocyst(e)ine.

Plasma levels of homocysteine have been actively researched as a risk factor for CVD, initially based on the observation that patients with hereditary homocystinuria, an inborn error of metabolism associated with high plasma levels of homocysteine, had a markedly increased risk of CVD. Subsequently, prospective epidemiologic studies were conducted to determine if an elevated plasma level of homocysteine was an independent risk factor for CVD and could be used to improve current risk prediction models. Several case-control studies have also suggested that elevated homocysteine is a risk factor for venous thromboembolism (VTE; pulmonary embolism, deep vein thrombosis).

Interest in homocysteine as a potentially modifiable risk factor has been stimulated by the epidemiologic finding that levels of homocysteine are inversely correlated with levels of folate. This finding has raised the possibility that treatment with folic acid might lower homocysteine levels and, in turn, reduce the risk of CVD and thrombotic events. Therefore, homocysteine has potential utility both as a risk predictor and as a target of treatment.

Determination of homocysteine concentration may be offered as a component of a comprehensive cardiovascular risk assessment that may include evaluation of small-density lipoproteins, subclassification of high-density lipoproteins, evaluation of lipoprotein (A), high-sensitivity C-reactive protein, and genotyping of apolipoprotein E. Determination of homocysteine concentration may also be offered as part of risk assessment for patients at high risk of VTE events or who have experienced idiopathic VTE, recurrent VTE, thrombosis occurring at a young age, or thrombosis at an unusual site.

**Regulatory Status**

Several homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA product code: LPS. Examples are listed in Table 1.
### Table 1. Homocysteine Test Systems

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Cleared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine Enzymatic Assay</td>
<td>Roche Diagnostics</td>
<td>2012</td>
</tr>
<tr>
<td>Diazyme Enzymatic Homocysteine Assay</td>
<td>Diazyme Laboratories</td>
<td>2012</td>
</tr>
</tbody>
</table>

### Rationale

This evidence review was created in May 2001 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 7, 2017.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

### Cardiovascular Disease

#### Clinical Context and Test Purpose

The purpose of testing homocysteine levels in asymptomatic patients at risk of cardiovascular disease (CVD) or in patients who have CVD is to inform management decisions such as whether to lower homocysteine levels.

The question addressed in this evidence review is: Does homocysteine testing of asymptomatic patients at risk of CVD or of patients who have CVD improve health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant populations of interest are individuals who are asymptomatic with risk of CVD and those who have CVD.

**Interventions**

The relevant intervention of interest is homocysteine testing.

**Comparators**

The relevant comparator of interest is routine care without homocysteine testing.
**Outcomes**
The general outcomes of interest are test accuracy and validity, other test performance measures, and change in disease status. Morbid events attributable to CVD, including stroke and myocardial infarction, may also be assessed.

**Timing**
The time frame for an outcome varies from 1 to 2 years, for assessment of hypertension or vascular changes, to 3 or more years, for assessment of coronary artery disease or stroke events.

**Setting**
Patients with or at risk of CVD may be assessed in the outpatient setting by a primary care medical provider or a specialist managing CVD.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
In 2002, the Homocysteine Studies Collaboration published a meta-analysis of observational studies evaluating the association between homocysteine concentration and risk of ischemic heart disease (IHD) or stroke.³ Thirty studies were identified that had individual patient data available; this included 18 retrospective studies and 13 prospective studies. In the prospective studies, blood for measuring homocysteine concentration was collected before the clinical onset of disease. The adjusted odds ratio of IHD associated with a 25% lower homocysteine level was 0.83 (95% confidence interval [CI], 0.77 to 0.89) in prospective studies, 0.67 (95% CI, 0.62 to 0.71) in retrospective studies using population controls, and 0.73 (95% CI, 0.64 to 0.83) in retropectives studies with other controls. The adjusted odds ratio of stroke associated with a 25% lower homocysteine level was 0.77 (95% CI, 0.66 to 0.90) in prospective studies, 0.86 (95% CI, 0.73 to 1.01) in retrospective studies with population controls, and 0.46 (95% CI, 0.30 to 0.70) in retrospective studies with other controls. The risk of IHD and stroke was significantly weaker in the prospective studies than in the retropectives studies, which may reflect biases in retrospective studies.

Subsequent meta-analyses of observational studies have found significant associations between homocysteine and morbidity and mortality, including a 2015 meta-analysis of 12 studies, which reported increased coronary artery disease, CVD, and all-cause mortality with higher homocysteine levels.²

Among the prospective studies included in the Homocysteine Studies Collaboration meta-analysis was one by Folsom et al (1998) that identified patients who developed congenital heart disease (CHD) among an initial cohort of 15,792
patients participating in the Atherosclerosis Risk in Communities trial. Median follow-up time was 3.3 years. Plasma homocysteine was evaluated from the stored blood samples of the 232 patients plus a random sample of the rest of the cohort. While homocysteine was a significant univariate predictor of coronary artery disease, this association was not statistically significant after adjusting for other cardiac risk factors in multivariate analysis. Another prospective study was published by Evans et al (1997). They identified 240 cases of nonfatal myocardial infarction (MI) or coronary death among a cohort of 12,866 men participating in the Multiple Risk Factor Intervention Trial (MRFIT). Homocysteine from stored blood samples of these patients plus 472 control patients were evaluated. With a follow-up ranging from 11 to 17 years, homocysteine levels did not appear to be an independent risk factor for CHD. In contrast, in a nested case-control study derived from a prospective cohort of 21520 men enrolled in the British United Provident Study, Wald et al (1998) reported that the initial stored plasma level of homocysteine was significantly higher among 229 men who ultimately died of IHD compared with a control group of 1126 men who did not die of IHD and did not have a history of IHD.

Representative studies on the association between homocysteine and various types of CVD are described in Table 2.

### Table 2. Individual Studies of Homocysteine and CVD Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcomes</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al (2010)</td>
<td>6371 individuals ages 40-79 y without history of MI, stroke, or PAD; 3860 (61%) with homocysteine level available</td>
<td>10-y CVD risk based on FRS:</td>
<td>Homocysteine levels at ≥85th percentile associated with high FRS: OR=2.1 (95% CI, 1.48 to 3.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low risk (n=2527)</td>
<td>Homocysteine levels at ≥85th percentile not significantly associated with intermediate FRS: OR=1.11 (95% CI, 0.89 to 1.38)</td>
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<tr>
<td></td>
<td></td>
<td>Intermediate risk (n=3336)</td>
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<tr>
<td></td>
<td></td>
<td>High risk (n=508)</td>
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</tr>
<tr>
<td>Wang et al (2014)</td>
<td>5935 individuals with hypertension enrolled in a population-based prospective cohort study</td>
<td>Incident ischemic stroke, CHD</td>
<td>Homocysteine levels ≥30 µmol/L (vs &lt;15 µmol/L) associated with higher ischemic stroke rates after adjusting for ischemic stroke risk factors: OR=2.86 (95% CI, 1.72 to 4.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Homocysteine levels ≥30 µmol/L (vs &lt;15 µmol/L) not associated with CHD</td>
</tr>
<tr>
<td>Han et al (2015)</td>
<td>5488 individuals with follow-up from a population-based prospective cohort study of 5935 hypertensive individuals</td>
<td>Incident ischemic stroke</td>
<td>Homocysteine levels ≥15 µmol/L associated with higher ischemic stroke rates: HR=2.18 (95% CI, 1.65 to 2.89)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Among 501 subjects who took folic acid supplementation, plasma homocysteine levels declined an average 6.7 µmol/L (clinical outcomes not reported separately)</td>
</tr>
<tr>
<td>Wang et al (2015)</td>
<td>200 cases with hypertension and ischemic stroke, vs</td>
<td>Incident stroke</td>
<td>After adjusting for ischemic stroke risk factors, total homocysteine associated with ischemic stroke</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Outcomes</td>
<td>Major Findings</td>
</tr>
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<tr>
<td>Catena et al (2015)</td>
<td>562 consecutive patients with hypertension evaluated at a single center</td>
<td>Prevalence of:</td>
<td>After adjusting for confounding variables, homocysteine significantly associated with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Metabolic syndrome</td>
<td>- Presence of metabolic syndrome: OR=1.01 (95% CI, 1.00 to 1.02; p=0.02)</td>
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<td></td>
<td></td>
<td>- CHD</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Cerebrovascular disease</td>
<td>- Presence of cerebrovascular disease or CVD: OR=1.011 (95% CI, 1.00 to 1.02; p=0.01)</td>
</tr>
<tr>
<td>Sheng et al (2015)</td>
<td>1680 subjects with arterial stiffness measurements enrolled in a community-based cross-sectional study</td>
<td>Vascular function measures:</td>
<td>Homocysteine levels positively correlated with: CF-PWV (r=0.211, p&lt;0.001) and CA-PWV (r=0.148, p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CF-PWV</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- CA-PWV</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Heart rate-corrected AI</td>
<td>Levels negatively correlated with AI (r = -0.052, p=0.016)</td>
</tr>
<tr>
<td>Shi et al (2015)</td>
<td>3799 adults with ischemic stroke enrolled in a single hospital in China</td>
<td>Poststroke mortality</td>
<td>Among 223 patients who died during follow-up, those with highest 3rd and 4th quartiles of homocysteine had higher risk of stroke death, after adjusting for confounding variables:</td>
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<tr>
<td></td>
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<td>- 3th vs 1st quartile: adjusted HR=2.27 (95% CI, 1.06 to 4.86; p=0.029)</td>
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<td></td>
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<td>- 4th vs 1st quartile: adjusted HR=2.15 (95% CI, 1.01 to 4.63; p=0.049)</td>
</tr>
<tr>
<td>Shoamanesh et al (2016)</td>
<td>3224 adults from Framingham Offspring Cohort (community-dwelling sample)</td>
<td>Incident ischemic stroke</td>
<td>After adjusting for SBP, hypertension treatment, current smoking, diabetes, CVD, and atrial fibrillation, total homocysteine associated with incident ischemic stroke: HR=1.20 (95% CI, 1.01 to 1.43)</td>
</tr>
</tbody>
</table>

AI: augmentation index; CA-PWV: carotid-ankle pulse wave velocity; CF-PWV: carotid-femoral pulse wave velocity; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; FRS: Framingham Risk Score; HR: hazard ratio; MI: myocardial infarction; OR: odds ratio; PAD: peripheral arterial disease; SBP: systolic blood pressure.

For patients with known CVD, prospective data have more consistently demonstrated that homocysteine is a risk factor for future events. For example, Nygard et al (1997) reported on a prospective study of the plasma homocysteine levels in 587 patients with angiographically confirmed coronary artery disease. After a median follow-up of 4.6 years, authors compared the initial homocysteine levels of the 64 (10.9%) patients who had died with those of the remaining 523 survivors. The authors reported a strong graded dose-response relation between plasma homocysteine and mortality. In addition, Knekt et al (2001) reported on outcomes at 13-year follow-up for 3471 middle-aged Finnish men, 884 of whom had known CVD at baseline. Using the homocysteine levels from stored blood
samples, a strong positive correlation was noted between homocysteine concentration and subsequent major coronary events in men with known CVD at baseline. However, investigators found no association between serum homocysteine concentration and the incidence of major coronary events (death from CHD, nonfatal MI) among men originally free of heart disease.

In 2011, Veeranna et al published a post hoc analysis of national survey databases to evaluate whether adding homocysteine to the Framingham Risk Score (FRS) model improves risk classification.\textsuperscript{16} Data were taken from the nationally representative Multi-Ethnic Study of Atherosclerosis (MESA) survey, which included subjects between the ages of 45 and 84 years with no history of CVD, and the National Health and Nutrition Survey III (NHANES III), a sample of noninstitutionalized subjects. Homocysteine level was associated with CVD risk in both databases. In a receiver operating characteristic curve analysis, the area under the curve for predicting CHD events in the MESA database was 0.74 using the FRS and 0.76 when homocysteine level was added to the FRS. The improvement in risk prediction was statistically significant ($p<0.001$). The area under the curve for predicting CHD deaths in NHANES III was 0.84 using the FRS alone and 0.87 when homocysteine level was added to the FRS; this difference was also statistically significant ($p<0.001$). Adding homocysteine to the FRS model resulted in the reclassification of 832 (12.9%) subjects in the MESA cohort and 1243 (18%) in the NHANES III cohort. This study did not address whether testing for homocysteine would improve health outcomes.

A 2016 prospective study by Ma et al assessed 30-day outcomes in 805 patients who were admitted to a single center for treatment of acute MI; 348 patients had low homocysteine levels (<15 mmol/L), and 457 patients had homocysteine levels greater than 15 mmol/L.\textsuperscript{17} The groups were compared for incidence of 5 adverse cardiac events (angina pectoris, reinfarction, heart failure [Killip class II-IV], cardiac rupture, death); of these end points, three were more prevalent in the high homocysteine group than in the low homocysteine group. Heart failure occurred in 44 (9.6%) of the high homocysteine group, but only 8 (2.3%) of the low homocysteine group ($p<0.001$); cardiac rupture occurred in 16 (3.5%) of the patients with high homocysteine levels, compared with 4 (1.1%) of those with low levels ($p=0.03$). Differences were also found between the low- and high-Hcy groups for the end points of death (2.3% vs 7.9%; $p<0.001$) and total adverse outcomes (22.8% vs 11.8%; $p<0.001$); however, no significant difference was found for either angina pectoris or reinfarction ($p=0.45$ and $p=0.65$, respectively). As independent predictors of adverse events following acute MI, age and homocysteine levels were determined to have significant odds ratios (OR; OR=2.114; 95% CI, 1.416 to 3.156; $p<0.001$; OR=2.055; 95% CI, 1.376 to 3.068; $p<0.001$, respectively). The authors acknowledged a lack of data on potential “pathogenic mechanisms” in the association between homocysteine levels and adverse cardiac events, recommending that future studies include a larger study sample and longer follow-up.
**Section Summary: Clinically Valid**
A meta-analysis of observational studies found a moderately statistically significant association between homocysteine levels and risk of CVD. One study analyzing nationally representative survey data found that adding homocysteine level to the FRS significantly improved risk prediction.

Studies have also found a significant correlation between homocysteine levels in patients with known CVD and subsequent coronary events. One study analyzing nationally representative survey data found that adding homocysteine level to the Framingham risk score significantly improved risk prediction. Overall, the available evidence has suggested that homocysteine levels are associated with increased risk of a variety of cardiovascular disorders and outcomes among patients with existing CVD.

**Clinically Useful**
Assessing whether the use of homocysteine in clinical practice to manage CVD has clinical utility requires demonstrating that identification of homocysteine levels leads to changes in patient management that improve patient outcomes.

Vitamin B and folic acid supplementation are potential interventions that could be used for patients with high homocysteine levels to improve health outcomes. However, public health measures are already in place that require all enriched grain products be fortified with folic acid to reduce the risk of neural tube defects in newborns. This fortification has been associated with a decrease in plasma homocysteine concentration in a population-representative adult sample. Trials evaluating the impact of homocysteine-lowering therapy on health outcomes should thus evaluate the utility of treatments that lower homocysteine levels beyond those achieved by these general public health measures. In addition, clear target levels for homocysteine concentration would need to be established for translating information on homocysteine lowering into clinical practice.

Numerous randomized controlled trials (RCTs) have provided evidence on the benefit of vitamin therapy to reduce homocysteine levels and prevent cardiovascular (CV) events. Moreover, several meta-analyses have synthesized the available RCT evidence assessing the impact of vitamin therapy on homocysteine levels and CV events.

**Systematic Reviews**
A 2016 meta-analysis of RCTs evaluated homocysteine-lowering therapy with B vitamins for reducing the risk of subsequent stroke among high CVD risk individuals who were not taking antiplatelet medications. Reviewers included 3 trials from 1966 to April 2015 that had at least 1 year of follow-up with stroke as the primary outcome: The Vitamin Intervention for Stroke Prevention (VISP) trial, the VITAmins TO Prevent Stroke (VITATOPS) trial, and the Heart Outcomes Prevention Evaluation (HOPE) 2 trial. The meta-analysis included 4643 participants (1773 in VISP, 1463 in VITATOPS, 1407 in HOPE-2) who were not taking antiplatelet agents at baseline. There was no evidence of heterogeneity for the stroke outcome. Those taking vitamin B supplementation had a lower risk of
recurrent stroke (hazard ratio [HR], 0.71; 95% CI, 0.58 to 0.88) compared with controls (low-dose supplementation or placebo). In VITATOPS, participants not on antiplatelet therapy were more likely to be East Asian. In HOPE-2, the effect of supplementation on stroke was highest in those with hyperhomocysteinemia or residing in a country without food fortification. Therefore, it is not clear whether the effect of homocysteine-lowering therapy on stroke risk in those not on antiplatelets would apply to a U.S. population.

In 2015, a Cochrane systematic review (originally published in 2009 and updated in 2013\textsuperscript{20}) on the effectiveness of homocysteine-lowering interventions for preventing CV events, including both MI and stroke, was again updated.\textsuperscript{21} Reviewers included RCTs assessing the effects of homocysteine-lowering interventions for preventing cardiovascular events with at least 1 year of follow-up and considered MI and stroke as the primary outcomes. No new trials published since the last update were identified. Twelve trials (total N=47,429 subjects) met eligibility criteria. Nine included more than 1000 participants. Nine studies used placebo controls, two used usual care controls, and one compared high with low doses of homocysteine-lowering therapy. In a pooled analysis of 11 trials, there was no statistically significant difference in nonfatal or fatal MI between intervention and control groups (relative risk [RR], 1.02; 95% CI, 0.95 to 1.10). In a pooled analysis of 9 studies, there was no significant difference between groups in the rate of nonfatal or fatal stroke (RR=0.91; 95% CI, 0.82 to 1.00). There was also no significant mortality benefit in groups assigned to homocysteine-lowering therapy. For mortality of any cause, the RR was 1.01 (95% CI, 0.96 to 1.07) in a meta-analysis of data from 10 trials.

In 2011 Zhou et al conducted a systematic review of double-blind placebo-controlled randomized trials evaluating the impact of folic acid supplementation on CV outcomes.\textsuperscript{22} Interventions were included if they involved supplementation with vitamin B in addition to folic acid. Reviewers selected only trials that included at least 100 patients and had at least 6 months of follow-up. Of 66 articles retrieved, 16 trials with data on 44,841 patients met reviewers’ inclusion criteria. In a meta-analysis of findings from 12 trials, folic acid supplementation did not have a significant effect on major CV events compared with placebo (RR=0.98; 95% CI, 0.93 to 1.04). In addition, folic acid supplementation did not have a significant effect on individual outcomes including stroke (12 trials; RR=0.89; 95% CI, 0.78 to 1.01), MI (11 trials; RR=1.00; 95% CI, 0.93 to 1.07), or all-cause mortality (14 trials; RR=1.00, 95% CI, 0.96 to 1.05).

Also in 2011, Clarke et al published a meta-analysis of placebo-controlled homocysteine-lowering randomized trials.\textsuperscript{23} This meta-analysis selected studies that included at least 1000 participants and had at least 1 year of follow-up. Eight trials (total N=37,485 individuals) met reviewers’ inclusion criteria. In a pooled analysis of findings from the 8 trials, vitamin B supplementation did not have a significant effect on risk of CHD events compared with placebo (RR=1.01; 95% CI, 0.96 to 1.07). In addition, in pooled analyses of data from the 8 trials, vitamin B supplementation did not have a significant effect on stroke events (RR=0.96; 95%
CI, 0.87 to 1.07), cancer events (RR=1.08; 95% CI, 0.99 to 1.17), or all-cause mortality (RR=1.02; 95% CI, 0.97 to 1.07).

A 2012 meta-analysis by Huang et al assessed RCTs evaluating vitamin B supplementation in patients with preexisting vascular disease. This review had more lenient inclusion criteria because there was no limitation on study size or intervention duration. Nineteen trials (total N=47,921 patients) were selected for the meta-analysis. In a pooled analysis of study data, reviewers found a statistically significant benefit of vitamin B supplementation on stroke (RR=0.88; 95% CI, 0.82 to 0.95). Similar to the other meta-analyses, vitamin B supplementation did not have a statistically significant impact on other outcomes, including CHD, MI, and all-cause mortality. Given the more relaxed entry criteria, the meta-analysis might have included lower quality studies; reviewers did not present a formal analysis of trial quality.

A 2014 meta-analysis included RCTs that compared folic acid supplementation (at least 5 mg/d for at least 4 weeks), without vitamin B supplementation, with placebo and evaluated endothelial function and homocysteine levels as outcomes in patients with coronary artery disease. Six trials (total N=377 subjects) were included. In the pooled analysis, folic acid supplementation was associated with increased flow-mediated dilation, a noninvasive, ultrasound-based method to assess vascular endothelial function (mean difference [MD], 57.72 μm; 95% CI, 50.14 to 65.3 μm; p<0.05). Folic acid supplementation was also associated with reduced plasma homocysteine concentration (MD = -3.66 μmol/L; 95% CI, -5.44 to -7.87 μmol/L; p<0.05). For other measures of endothelial function, there was no significant change in the response to end diastolic diameter, glyceryl-trinitrate diameter, heart rate, baseline and peak hyperemic flow, or systolic and diastolic blood pressure between the folic acid and placebo groups.

Liu et al (2014) also reported results of a meta-analysis of placebo-controlled randomized trials that evaluated the effect of homocysteine-lowering therapies on flow-mediated dilation in patients with coronary artery disease. Eight studies (total N=611 subjects) were included; folic acid doses ranged from 400 to 10,000 μg/d. In the pooled analysis, folic acid supplementation was associated with improved flow-mediated dilation compared with placebo (standardized MD=1.65; 95% CI, 1.12 to 2.17; p<0.001), but there was significant heterogeneity across studies.

**Randomized Controlled Trials**

Representative RCTs evaluating homocysteine-lower interventions are described next. The HOPE-2 trial (2006) included 5522 patients with preexisting vascular disease. Patients were randomized to a regimen of folate, vitamin B₆, plus vitamin B₁₂ or placebo and followed for an average of 5 years. There were no significant differences in the composite outcome of CV death, MI, or stroke (RR=0.95; 95% CI, 0.84 to 1.07). However, there was a significant decrease in the risk of stroke for patients in the treatment group (RR=0.75; 95% CI, 0.59 to 0.97; p=0.03). For the secondary outcome of hospitalization for unstable angina, a significantly
increased risk was reported for the treatment group (RR=1.24; 95% CI, 1.04 to 1.49; p=0.02).

The 2006 Norwegian Vitamin Trial (NORVIT) enrolled 3749 patients with a recent MI who were randomized to combinations of folate and/or B vitamins. Patients were followed for a mean of 3.3 years for the primary outcome (a composite of recurrent MI, stroke, and sudden cardiac death). For patients assigned to the active treatment groups, no significant reductions were noted for any of the primary or secondary outcomes. For patients assigned to the combined folate/vitamin B6/vitamin B12 group, a marginally significant increased risk (RR=1.22; 95% CI, 1.00 to 1.50; p=0.05) was observed for the primary composite outcome group.

In 2010, findings from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine in the U.K. were reported. A total of 12,064 adults with a history of MI were randomized to folic acid plus vitamin B12 or placebo. An additional eligibility criterion was blood cholesterol of at least 135 mg/dL if taking a statin or 174 mg/dL otherwise. Before randomization, patients participated in a run-in period to confirm adherence to treatment. After 3 to 4 years of follow-up, due to the low number of major coronary events in the treatment group, the steering committee (blinded to interim between-group outcomes) changed the primary outcome from major coronary events to major vascular events. This composite variable included nonfatal MI, death from CHD, fatal or nonfatal stroke, or any arterial revascularization. After a mean follow-up of 6.7 years, vitamin treatment was not associated with a statistically significant reduction in the primary outcome. The number of major vascular events were 1537 (25.5%) in the vitamin group and 1493 (24.8%) in the placebo group (RR=1.04; 95% CI, 0.97 to 1.12). There were no significant differences in risk for any of the components of the composite outcome. In addition, death from all causes did not differ significantly between groups; there were 983 (16.3%) deaths in the vitamin group and 951 (15.8%) in the placebo group (RR=1.04; 95% CI, 0.96 to 1.13).

van Dijk et al (2015) reported on the results of the B-PROOF trial, an RCT comparing B vitamins (vitamin B12 500 mg, folic acid 400 mg) with placebo for improving CV outcomes among elderly patients with hyperhomocysteinemia. The trial included 2929 subjects over age 65 with an elevated homocysteine levels (12–50 µmol/L) who were randomized to 2 years of B-vitamin therapy (n=1458) or placebo (n=1461). A random sample of participants (n=569) underwent baseline vascular measurements. Within the vascular subgroup, the aortic pulse pressure after 2 years of intervention was significantly higher in the B-vitamin treatment group (49.6 mm Hg) than in the placebo group (47.2 mm Hg; p=0.02). However, aortic-femoral pulse wave velocity and carotid intima-media thickness did not differ significantly between groups. In the vascular subgroup, serum homocysteine increased by 0.6 µmol/L in the placebo group but decreased by 3.6 µmol/L in the B-vitamin therapy group. In the entire study population, the treatment groups did not differ significantly in terms of blood pressure or hypertension incidence, CV
event incidence, or MI incidence. In subgroup analyses, among women, treatment group subjects had a lower incidence of CV events than placebo group subjects (OR=0.33; 95% CI, 0.15 to 0.71).

**Section Summary: Cardiovascular Disease**
Numerous large placebo-controlled randomized trials have evaluated the impact of folic acid plus vitamin B supplementation on risk of cardiovascular events, including MI and stroke. With few exceptions, meta-analyses of these RCTs have found that homocysteine-lowering interventions have not had a statistically significant effect on the rate of major CV events. Two meta-analyses of RCTs reported that homocysteine-lowering interventions have been associated with improvements in a measure of vascular endothelial function, but it has not been shown that these changes are associated with improved clinical outcomes.

**Venous Thromboembolic Disorders**

**Clinical Context and Test Purpose**
The purpose of testing homocysteine levels in asymptomatic patients at risk of venous thromboembolism (VTE) or of patients who have VTE events is to inform management decisions such as whether to lower homocysteine levels.

The question addressed in this evidence review is: Does homocysteine testing of asymptomatic patients at risk of VTE or of patients who have had previous VTE events improve health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant populations of interest are individuals who are asymptomatic with the risk of VTE and those who have had VTE events.

**Interventions**
The relevant intervention of interest is homocysteine testing.

**Comparators**
The relevant comparator of interest is routine care without homocysteine testing.

**Outcomes**
The general outcomes of interest are test accuracy and validity, other test performance measures, and change in disease status. Morbid events associated with VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), may be studied.

**Timing**
The time frame from outcomes varies but it is expected to be 3 or more years for assessment of DVT or PE.
**Setting**
Patients with or at risk of VTE may be assessed in the outpatient setting by a primary care medical provider or a specialist managing VTE.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist.

**Clinically Valid**
Den Heijer et al (2005) published a meta-analysis of observational studies on the relation between homocysteine and risk of venous thrombosis. Thirty-one retrospective studies (n=3289 patients) and 3 prospective studies (n=476 patients) published before July 2003 were included. A 5 µmol/L higher total plasma homocysteine level was associated with a 27% (95% CI, 1% to 59%) higher risk of venous thrombosis in prospective studies and a 60% (95% CI, 10% to 134%) higher risk in retrospective studies. Selected studies had varying cutoffs for high homocysteine and a mix of first-time and recurrent VTE. Two earlier systematic reviews reached similar conclusions on the association between homocysteine and risk of VTE.\(^{32,33}\)

Several studies have examined the risk of VTE in patients with both homocysteinemia and an inherited thrombophilia (eg, factor V Leiden), with mixed results. Keijzer et al (2007) performed a meta-analysis of the interaction between factor V Leiden and hyperhomocysteinemia.\(^{34}\) In 5 observational studies (825 patients with venous thrombosis, 2109 controls), there was no evidence for additive or multiplicative interaction between factor V Leiden and hyperhomocysteinemia. The relative excess risk due to additive interaction was \(-1.77\) (95% CI, \(-8.61\) to 5.08) and multiplicative interaction term was \(0.86\) (95% CI, 0.35 to 2.14).

Following the systematic reviews, a 2008 case-cohort from the large Norwegian Health Study of Nord-Trøndelag (HUNT2) study prospectively investigated whether elevated plasma homocysteine levels before the event were associated with subsequent first VTE in a general population.\(^{45}\) VTE was identified in 505 patients, and 1458 age- and sex-matched controls were selected for the case-cohort study from the original cohort of 66,140 HUNT2 participants. Serum total homocysteine blood was collected between 1995 and 1997, a median of 33 months before the events. The odds for VTE for homocysteine levels above vs below the 95th percentile was \(1.50\) (95% CI, 0.97 to 2.30). Results were similar after control for age, predisposing risk factors, or time to event. The association was limited to men (OR=2.17; 95% CI, 1.20 to 3.91); no association was found in women (OR=1.00; 95% CI, 0.52 to 1.92). There was not a dose-response relation between VTE and homocysteine.
Section Summary: Clinically Valid
A meta-analysis of observational studies found a statistically significant moderate association between homocysteine levels and risk of VTE. However, a subsequent large prospective study found the risk to be only increased in men. The available evidence has suggested that homocysteine levels may be associated with increased risk of VTE in the general population.

Clinically Useful
A systematic review of observational studies, along with 2 RCTs, have provided evidence relevant to the discussion of vitamin therapy to reduce homocysteine levels and prevent VTE.

Systematic Reviews
Zhou et al (2012) published a systematic review of observational studies on the association between B-group vitamins and VTE.\(^{36}\) Five studies relating to the effects of B-group vitamins supplementation on VTE prevention were selected. The studies included an uncontrolled interventional study in patients with homocystinuria, an observational study of pregnant women, a trial with measured homocysteine levels as the primary outcome, a secondary analysis of the HOPE-2 trial, and a secondary prevention trial. Reviewers did not perform a meta-analysis due to varying study designs and different baseline homocysteine levels. The uncontrolled study in patients with homocystinuria and the study in pregnant women both found an association between supplementation and decreased risk of VTE. The trial with homocysteine levels as an outcome showed that supplementation with a multivitamin (folic acid 5 mg, vitamin \(B_{12}\) 0.4 mg, vitamin \(B_6\) 50 mg) reduced homocysteine levels in patients with recurrent VTE and in healthy volunteers. The 2 trials with VTE outcomes are detailed in the following section.

Randomized Controlled Trials
The Vitamins and Thrombosis (VITRO) RCT (2007) evaluated the effect of homocysteine lowering by daily supplementation with B vitamins on the risk reduction of DVT and PE.\(^{37}\) Patients between 20 and 80 years of age with a first DVT or PE in the absence of major risk factors and a homocysteine concentration above the 75th percentile of a reference group were eligible (the hyperhomocysteinemic group). A second group of patients with a homocysteine below the 75th percentile of the reference group (called the normohomocysteinemic [placebo] group) were also enrolled. Patients were randomized to daily multivitamin supplementation of folic acid 5 mg, pyridoxine 50 mg, plus cyanocobalamin 0.4 mg, or to a placebo. Follow-up continued for 2.5 years. The primary outcome was objectively diagnosed recurrent DVT or PE. A total of 701 patients were enrolled (360 in the hyperhomocysteinemic group, 341 in the normohomocysteinemic group). Of the 353 assigned to the vitamin group, 43 events were observed (54/1000 person-years). In the 348 assigned to the placebo group, 50 events were observed (64/1000 person-years). The HR did not differ statistically significantly from 1 (HR=0.84; 95% CI, 0.56 to 1.26). There was no statistically significant reduction in recurrent VTE in the 360 patients with baseline homocysteine levels above the 75th percentile (HR=1.14; 95% CI, 0.65
to 1.98), or in the 341 patients with normal homocysteine levels (HR=0.58; 95% CI, 0.31 to 1.07).

The HOPE-2 trial (2007) evaluated whether long-term supplementation with folic acid, vitamin B$_6$, and vitamin B$_{12}$ aimed at lowering homocysteine levels would reduce the rates of major fatal and nonfatal CV events in patients with established CVD and/or diabetes. HOPE-2 was conducted at 145 clinical centers in 13 countries and enrolled 5522 patients 55 years of age or older with known CVD or diabetes and at least 1 other risk factor for vascular disease. Baseline information on previous VTE was not available. A secondary analysis from the HOPE-2 trial evaluated whether supplementation could reduce the risk of symptomatic VTE. VTE occurred in 88 patients during a mean 5-year follow-up. There was no effect of vitamin supplementation on rates of VTE in the total population (HR=1.01; 95% CI, 0.66 to 1.53) or in the 821 patients with baseline homocysteine levels in the highest quartile (>13.8 µmol/L) in the study (HR=1.71; 95% CI, 0.48 to 6.06).

**Section Summary: Venous Thromboembolic Disorders**

Two placebo-controlled randomized trials have evaluated the impact of folic acid and vitamin B supplementation on risk of VTE. Homocysteine-lowering interventions did not have a statistically significant effect on the rate of VTE in patients with previous VTE or in patients unselected for previous VTE but with CVD. Based on these trials, there is insufficient evidence to conclude that supplementation to reduce homocysteine will reduce the risk of VTE.

**Summary of Evidence**

For individuals who are asymptomatic with risk of CVD or individuals with CVD who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and CVD risk, especially in patients with preexisting vascular disease. However, evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins improves cardiovascular outcomes. Numerous large RCTs and meta-analyses of these trials have consistently reported that homocysteine-lowering treatment is ineffective in reducing major cardiovascular events. One systematic review, with a subgroup analysis of patients from 3 RCTs who were not on antiplatelet therapy at baseline, found that homocysteine-lowering treatment reduced the risk of stroke in that group. However, replication of this effect in countries with grain enriched with folic acid would be needed. Given the large amount of evidence from placebo-controlled randomized trials that homocysteine-lowering interventions do not improve health outcomes, it is unlikely that routine homocysteine testing has the potential to change management that improves health outcomes. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who are asymptomatic with risk of VTE or have experienced VTE events who receive homocysteine testing, the evidence includes of observational
studies and RCTs of homocysteine-lowering interventions. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. Observational evidence has generally supported the association between homocysteine levels and VTE risk, although the association was specific to men in the largest prospective study. However, evidence from RCTs evaluating homocysteine-lower interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces risk of VTE. Only a single RCT was designed to test for VTE as a primary outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

Cardiovascular Disease

National Institute for Health and Care Excellence
In 2016, the National Institute for Health and Care Excellence updated its guidance on risk assessment and reduction of cardiovascular disease (CVD), including lipid modification. The guidance asserted that full formal risk assessments should use a combination of risk assessment tools as well as informed clinical judgment. Homocysteine testing was not mentioned.

American Heart Association and American Stroke Association
In 2014, the American Heart Association and the American Stroke Association issued joint guidelines on the primary prevention of stroke. These guidelines were endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Preventive Cardiovascular Nurses Association. The guidelines stated that patients with hyperhomocysteinemia may be treated with B-complex vitamins to prevent ischemic stroke, but that the effectiveness was not clearly established (class IIb; level of evidence B).

American College of Cardiology and American Heart Association
In 2013, the American College of Cardiology and the American Heart Association issued joint guidelines on the assessment of arteriosclerotic cardiovascular risk (ASCVD). These guidelines were endorsed by 6 medical specialty associations. The guidelines developed multivariable equations to estimate age- and race-specific ASCVD risk. The equations included age, total and high-density cholesterol levels, systolic blood pressure, antihypertensive treatment use, diabetes history, and current smoking status. The use of homocysteine screening for assessing the risk of ASCVD was not considered in these guidelines.

National Academy of Clinical Biochemistry
In 2009, the National Academy of Clinical Biochemistry published guidelines on biomarkers for primary prevention of CVD. The Academy concluded that while homocysteine is a modest independent CVD risk factor, homocysteine screening for primary prevention and assessment in healthy individuals was unwarranted.
Venous Thromboembolism

Agency for Healthcare Research and Quality
In 2016, the Agency for Healthcare Research and Quality issued guidelines for effective quality improvement on preventing hospital-associated venous thromboembolism (VTE). The VTE prevention protocol recommended involves a VTE risk assessment, a bleeding risk assessment, and a clinical decision support on prophylactic choices. Homocysteine testing was not mentioned in these guidelines.

National Institute for Health and Care Excellence
In 2015, the National Institute for Health and Care Excellence updated its guidance on VTE in adults admitted to hospital. This guidance recommended that all patients be evaluated for VTE risk on hospital admission. Homocysteine testing was not mentioned in this guidance.

U.S. Preventive Services Task Force Recommendations
In 2009, the U.S. Preventive Services Task Force issued a recommendation statement that the evidence was insufficient to assess the benefits and harms of using nontraditional risk factors to screen asymptomatic adults with no history of coronary heart disease to prevent coronary heart disease events. Homocysteine was one of the nontraditional risk factors considered in the recommendation. The recommendation is currently being updated.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

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<td>NCT01956786</td>
<td>Efficacy of Amlodipine-Folic Acid Tablets on Reduction of Blood Pressure and Plasma Homocysteine in Patients With Mild to Moderate Hypertension, Hyperhomocysteinemia and Angiotensin-Converting Enzyme Inhibitor Intolerance</td>
<td>540</td>
<td>Feb 2014 (unknown)</td>
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NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References
6. Park CS, Ihm SH, Yoo KD, et al. Relation between C-reactive protein, homocysteine levels, fibrinogen, and lipoprotein levels and leukocyte and platelet counts, and 10-year risk for cardiovascular disease among healthy adults in the USA. Am J Cardiol. May 1 2010;105(9):1284-1288. PMID 20403480


**Billing Coding/Physician Documentation Information**

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**ICD-10 Codes**

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<td>I82.210-</td>
<td>Other venous embolism and thrombosis code range</td>
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<td>I82.91</td>
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<td>Z13.6</td>
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**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

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<td>7/1/16</td>
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<td>2/2017</td>
<td>The first policy statement on cardiovascular disease was changed to not medically necessary status. An investigational policy statement was added for homocysteine measurement in the evaluation of venous</td>
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thromboembolic disorders. The policy title was changed to “Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disorders”, and scope of review broadened to include venous thromboembolism.

7/1/17  No policy statement changes.
7/1/18  No policy statement changes.

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